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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,953	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59,61,62 and 70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,61,62 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

Claims 59, 61-62 and 70 are pending.

Applicants' amendment filed 20 November 2003, which amends claims 59, 62 and 70, and cancels claims 1-58, 60, 63-69 and 71-101, have been entered. Claims 59, 61-62 and 70 are pending to which the following is or remains applicable. Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Objection to Declaration under 37 C.F.R. 1.131

Declaration under 37 C.F.R. 1.131 filed 16 June 2003 has not been entered because it is unsigned.

Applicants' response to the objection

The response filed 20 November 2003 commends that the Rule 131 affidavit (filed 16 June 2003) and the Rule 132 affidavits (filed 16 June 2003) have been signed (see page 5). The applicants' comment has been considered but not persuasive because Examiner cannot find the signed declarations under 37 C.F.R. 1.132 and 1.132 in the current application file. Herein, Examiner has enclosed the two copies (dated 16 June 2003) of the declarations thereof which were unsigned by the indicated inventor(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

This is a New Matter rejection for the following reasons:

The amended claim 1 recites "selecting …" and "human subject" and claim 7 recites "human subject"; these recitations represent a departure from the specification and the claims as originally filed.

The specification does not appear to provide a clear support of "selecting …" and "human subject". The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 59, 61-62 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 recites "modulation"; the recitation is not clear as to whether or not the modulation refers to up- or down-regulation. The dependent claims are also rejected.

Claim 70 is indefinite because the recitation "a second pharmaceutical agent" is unclear as to (i) where in the claims the first pharmaceutical agent is recited? and (ii) whether or not the said pharmaceutical agent comprises the modulator recited in claim 59.

Response to the rejection under 35 USC 112, the second paragraph

The response filed 20 November 2003 argues that the term "modulation" is generic and covers both up- and down-regulation; there is nothing indefinite about this recitation (see page 3, the last paragraph). The applicants' argument is not persuasive because a method of up-regulation and a method of down-regulation are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct *agonists* or *antagonists* to accomplish these mutually exclusive endpoints, and because, one substance (modulator) cannot act as an agonist meanwhile as an antagonist. Thus, the method that is directed to use of such substance (modulator) has to be clarified as to which mechanism, agonist mechanism (up-regulation) or antagonist mechanism (down-regulation), the claimed method is directed,.

Also, the response asserts that the recitation "a second pharmaceutical agent" in the amended claim 70 would obviate the rejection (see page 4, the 3rd paragraph). The applicants'

argument is not persuasive because of the reason set forth in the above statement and because reciting addition of "second" before "pharmaceutical agent" in the claim does not obviate the rejection set forth above.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 59 and 61 are again rejected under 35 U.S.C. 102 (a) as being anticipated by Fuentes, J. J. *et al.* (*Human Mol. Genet.* (July 1, 2000) 9, 1681-1690).

Fuentes *et al.* teach *DSCR1* gene encoded protein DSCR1 (*i.e.,* MCP1), and teach that the DSCR1 involves regulation of muscle growth (see page 1681, the "*Introduction*" section). Fuentes et al. teach identifying (see page 1682) a modulator of DSCR1 protein, which is calcium. Also, Fuentes et al. teach that the *DSCR1* expression is induced by calcium through a calcineurin-dependent mechanism (see page 1687, the right column, the 2nd paragraph), and that calcium signaling regulates *DSCR1* expression in a human subject (see Figure 7) (see page 1687, the right column, the 2nd paragraph). Further, Fuentes et al. teach that the calcium is introduced into a human subject by calcium ionphore (see page 1688, "materials and Methods" section). The Fuentes et al. teachings are applied to the application claims 59 and 61.

Claims 59, 61 and 70 are again rejected under 35 U.S.C. 102 (a) as being anticipated by Rothermel, B. *et al.* (*J. Biol. Chem.*, (March 24, 2000) 275, 8719-8725).

Rothermel *et al.* teach a process of regulating mammalian myoblast growth by MCIP1 protein; the process comprises identifying a modulator (i.e., calcineurin) for MCIP1 expression which is indicated by activated calcineurin up-regulates subcellular distribution of MAIP1 during muscle differentiation, and *co-expression* of the polypeptide, *i.e.*, calcineurin, in myocytes promotes expression of MCIP1 protein in cytoplasm (see pages 8723-8724, and Figure 6). The Rothermel et al. teaching meets the limitations set forth in claims 59 and 61 of the instant application.

The current disclosure is also directed to a therapeutic method for treating muscle cells in a human subject comprising administering the subject a modulator of MCIP1 expression. Rothermel et al. teach administering a calcineurin antagonist polypeptide, i.e., cyclosporin, an inhibits action of calcineurin that up-regulates MCIP involved muscle growth or differentiation, for preventing a cardiac disease state (e.g., cardiac hypertrophy) in a subject (see page 8725, the left column, the second to the last paragraph), as applied to claim 70 of the current application.

Since the cyclosporin is an antagonist (see page 8725, the left column, the 2nd paragraph), the above Rothermel et al. teaching is applied to the application 62.

Response to the rejections under 35 USC 102(a)

The response filed 20 November 2003 asserts that the rejections under 35 USC 102 by the Fuentes et al. and the Rothermel et al. references should be withdrawn as applicants have submitted the Inventor's Declarations under 37 C.F.R. 1.131 and 1.132 (see pages 4-5). The

applicants' argument is fully considered but not persuasive because the said declarations are unsigned by the inventor(s) (see the above-stated "Objection to Declaration under 37 C.F.R. 1.131"); thus, the Declaration are not considered in this Office action.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59, 62 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chin, E. R. et al. (*Gene Dev.* (1998) 12, 2499-2509) taken with Rothermel, B. *et al.* (*J. Biol. Chem.* (2000) 275, 8719-8725).

Chin et al. teach a process of modulating skeletal and cardiac muscle cell growth comprising identifying a peptide modulator for *calcineurin*, i.e., cyclosporin, and administering the cyclosporin to a subject (see abstract and pages 2502-2503, the section "*administration of the*

calcineurin antagonist cyclosporin A to intact animal promotes slow-to-fast fiber transformation", and see also Figure 4), wherein the subject is human (see page 2506, the right column, the 3rd paragraph, and page 2507). The Chin et al. teaching is applied to claims 59 and 62 of the current application.

Also, Chin et al. teach that administering calcineurin antagonist cyclosporin (a pharmaceutical agent) to intact animal including human (see pages 2505-2506) and that the modulation stated above has medical application, *e.g.*, treating cardiac hypertrophy, a cardiac disease (see page 2506). The Chin et al. teaching is applied to claim 70 of the current application.

Chin et al. do not explicitly teach that the modulator for muscle growth has an effect on MCIP1 expression as claimed in claim 59.

Rothermel et al. teach that calcineurin modulates MCIP1 (myocyte-enriched calcineurin interaction protein 1) through a direct interaction of the calcineurin catalytic domain with MCIP1 protein (see abstract), and that calcineurin regulates MCIP1 expression through up-regulating subcellular distribution of MCIP1 during muscle differentiation. Also, Rothermel et al. teach that *co-expression* of the polypeptide, *i.e.*, calcineurin, in myocytes promotes expression of MCIP1 protein in cytoplasm (see pages 8723-8724, and Figure 6). The above Rothermel et al. teachings that establish that calcineurin is a modulator for MCIP1-expression which regulates muscle growth, as applied to claim 59.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the above reference teachings because of the following reasons. (1) Chin et al. teach a process of modulating muscle cell growth in human subject comprising identifying the subject in need of muscle growth regulation, and identifying cyclosporin as a modulator for

muscle cell growth and differentiation administering to the subject the cyclosporin. (2) Rothermel et al. teach interaction between MCIP1 and an agonist of MCIP expression, i.e., calcineurin, significantly contributes to muscle growth. (3) Any modulator (agonist or antagonist) for calcineurin or/and MCIP1 has a regulatory effect on muscle growth, and any modulator that acts on calcineurin must regulate the MCIP1 expression since Rothermel et al. has established that calcineurin and MCIP1 are mutually interactive and regulated. (4) Cyclosporin, a potent antagonist to calcineurin therefore to MCIP1 expression for muscle growth, is a commonly used pharmaceutical agent (see page 2500, the right column, the 3rd paragraph, and pages 2502-2503 and 2506).

When combined, there would have been the following advantages: (i) calcineurin antagonist drug cyclosporin A has a therapeutic use in treating a muscle disorder state, e.g., cardiomyopathy, as taught by Rothermel et al. (se page 8725), and (ii) a signaling pathway involved in skeletal muscle growth is cyclosporin-sensitive (see abstract), as taught by Chin et al.

Given the above motivation, the skilled artisan would have combined the above reference teachings to develop the method of modulating muscle cell growth in a human subject comprising administering to the subject the identified drug (e.g., cyclosporin) that regulates MCIP1 expression through regulating a polypeptide modulator (e.g., calcineurin) of MCIP1 expression. Thus, the skilled artisan would have readily arrived at the current invention with successful expectation. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 59, 62 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sussman M. A. et al. (*Science* (1998) 281, 1690-1693) taken with Yang, J. et al. (*Cir. Res.* (2000) 87, e61-e68).

Sussman et al. teach a process of modulating cardiac muscle cell growth, e.g., preventing cardiac hypertrophy in mice comprising identifying a peptide modulator for calcineurin, i.e., cyclosporin, and administering the cyclosporin to the patient (see abstract, Figures 1-2, and pages 1690-1691 and 1693), wherein calcineurin is an activator for induction of MCIP1 expression as is evidenced by Yang et al. The Sussman et al. teaching is thus applied to claim 59 of the current application. Because cyclosporin is an antagonist of calcineurin, the above teaching is applied to the application claim 62. It is of note that the current invention is directed to a method of modulating muscle cell growth by administering to a subject a polypeptide modulator but NOT to a method of modulating MCIP1 expression, and that up-regulation of MCIP1 expression is an inherent property of calcineurin as is evidenced by the Yang's reference (see the above statement).

In addition, Sussman et al. teach that the cyclosporin therapy for cardiac disease, e.g., cardiac muscle hypertrophy, (see page 1690 and the last paragraph of 1693), as applied to claim 70 of the current application.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the above reference teachings because Sussman et al. teach a process of modulating muscle cell growth comprising administering to the subject the identified drug (e.g., cyclosporin) that regulates MCIP1 expression through modulating a polypeptide modulator (e.g., calcineurin) of MCIP1 expression which positively associates with the muscle growth. Thus, the

Sussman and Yang references meet the limitations set forth in claims 59, 62 and 70. Although Sussman's reference teach a mice model for the above-mentioned process and does not explicitly point out the subject is human, the Sussman et al. reference does teach that the established mouse models mimic intrinsic forms of *human* disease state (e.g. hypertrophic cardiomyophathy (HCM) that relates to an abnormal muscle cell, i.e., heart muscle cell that expresses myosin light chain-2 (see abstract and page 1692). Thus, the Sussman at el. reference meets the limitation set forth in claims 59 and 70 regarding "a human subject".

Thus, it would have been within an ordinary knowledge for the skilled artisan to readily extend the mouse model with respect to cyclosporin regulation of calciueurin/MCIP1 (myocyte-enriched calcineurin interaction protein 1) and thereby modulation of muscle growth in a human subject. The skilled artisan would have readily arrived at the current invention with successful expectation. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on

the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571 272-0949.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

January 14, 2004

ROBERT A. WAX
PRIMARY EXAMINER